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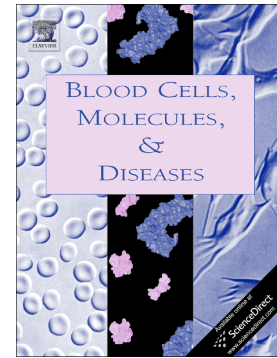
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Title: Prognostic Factors Associated with COVID-19 Related Severity in Sickle Cell Disease

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Short Running Headline: Predicting COVID-19 Severity in Sickle Cell Disease

Abstract

Background: Equipoise exists regarding sickle cell disease (SCD) as a risk factor for COVID-19 disease severity and variables that increase risk of COVID-19 severity in SCD. Given our health system's large SCD patient catchment, we analyzed our own experience in this regard.

Study Methods: Retrospective analysis of the clinical course and factors associated with need for hospitalization and ICU admission of SCD patients diagnosed with COVID-19 through the Northwell Health system from March 1 to Dec 31, 2020.

Results: Of 1098 patients with SCD, 3.3% were diagnosed with COVID-19. Overall rates of hospitalization, ICU admission, cohort mortality, and in-hospital mortality were 80%, 19%, 2.5% ,and 3.1%, respectively. By multivariable analysis, hospitalization risk was decreased by 60% for every 1 gm/dL increase in admission Hb. ICU admission risk was increased by 84% as a health care worker; increased by 45% for every 1000/uL increase in admission immature granulocyte count; and decreased by 17% with hydroxyurea use.

Discussion: High hospitalization rates are compatible with worsened severity upon COVID-19 infection in SCD compared to the general population. Patients should be placed on hydroxyurea to increase their Hb and perhaps lower their neutrophil counts. Health care workers with SCD may warrant special safety precautions.

Introduction

There is equipoise as to whether sickle cell disease (SCD) is a risk factor for disease severity with COVID-19. Some studies support that SCD increases risk for COVID-19 disease severity[1-6], whereas other studies do not.[7,8] Despite possible increased COVID-19 disease severity in SCD, one large study did not show an increased fatality rate in SCD[4]. Patient variables

associated with increased clinical severity of COVID-19 infection in SCD patients include older age[1,9], comorbidities[1,8-10], not being on hydroxyurea (HU)[1,9], history of stroke[2,8] and black race[5]. Non-SCD studies show similar risk factors such as older age[11,12], comorbidities[11,12], as well as being a health care worker (HCW)[13,14]. Possible laboratory-based predictors of hospitalization include the following admission values: high C-reactive protein (CRP)[1], low Hb[1,15,16], low lymphocyte count[1,15], high alanine aminotransferase[1], increased neutrophil-to-lymphocyte ratio[1,15], high immature granulocyte count (promyelocytes, myelocytes and metamyelocytes)[11,15,17], high creatinine[1], and high direct bilirubin[1]. Possible in-hospital mortality values include high D-dimer[1,11], high creatinine levels[1,9,11], high lactate dehydrogenase[1,11], and high CRP[11] on admission. Fewer comorbidities may contribute to the better outcome of pediatric patients with COVID-19 infection[9]. In order to add our experience in the prognosis of SCD patients with COVID-19, we analyzed the clinical course and potential variables associated with need for hospitalization and ICU admission in all SCD patients diagnosed with COVID-19 infection throughout the Northwell Health system between March 1 and Dec 31, 2020.

Materials and Methods

Study: This study was conducted under institutional review board approval at Northwell Health.

SCD patients: COVID-19 patients with SCD presenting between March 1 and Dec 31, 2020 were identified through Northwell's centralized electronic health record (EHR) system, which includes all patient data from 5 tertiary hospitals, 2 specialty hospitals and 7 community hospitals; this group includes the hospitals and their associated clinics caring for adult and pediatric SCD patients within the Northwell system as well as urgent care centers performing COVID-19 testing. The diagnosis of COVID-19 was determined by RT-PCR for SARS CoV-2

RNA on nasopharyngeal swab. The potential diagnosis of SCD was flagged by ICD-10 diagnosis or by a laboratory record of HbS $\geq 35\%$, and then confirmed by manual chart review to exclude the possibility of sickle cell trait. Northwell's overall catchment of unique SCD patients seen in 2020 was also enumerated through our EHR system using a HbS cutoff of $\geq 60\%$ in order to exclude patients with sickle cell trait, and HbC and HbS each $\geq 40\%$ to include Hb SC patients, as it was not feasible to manually review each patient record.

Retrospective chart review: Electronic and physical medical records of SCD patients with a diagnosis of COVID-19 were reviewed. Variables significant with previous publications or with scientific plausibility, and for which $\leq 10\%$ of values were missing, were recorded for further analysis; they are listed in *Supplementary Table 1*. Lab values were defined as baseline when they were measured during steady state at a previous visit unrelated to the current or other acute illness, and defined as admission when measured in the emergency department or upon admission for hospitalized patients and at the emergency department visit for outpatients. Baseline severity of SCD was assigned a numeric score (between 0-1) based on a validated SCD severity scoring system[18] based on gender; sickle genotype; steady-state systolic blood pressure, bilirubin, lactate dehydrogenase (LDH), mean corpuscular volume (MCV), white blood cell and reticulocyte count; history within the past year of acute chest syndrome, vaso-occlusive crisis, and chronic transfusion; and lifetime history of priapism, stroke, avascular necrosis, and sepsis. Attribution of respiratory symptoms to COVID-19 versus SCD was determined by the hospital team; COVID-19 severity was graded using a 5-tier method based on degree of respiratory involvement: asymptomatic, mild, moderate, severe and critical;[19]

Statistical analysis: R statistical software was used for all statistical analyses. Descriptive statistics were generated to characterize the study sample, non-parametric statistical tests were

run for between-group comparisons, and logistic regression models were conducted for univariate and multivariable analyses. Due to our small sample size, a variable was considered for inclusion in the multivariable analysis (MVA) if on univariate analysis the p-value was $p < 0.20$, unadjusted for multiple comparisons. Also, since admission rather than baseline variables may be more easily obtainable in real-world scenarios, admission values were preferred for MVA if both p-values met the $p < 0.20$ criteria. Finally, because multiple studies have looked at factors nonspecific to SCD that affect COVID-19 severity[12,15], more SCD-specific factors, such as sickle cell severity score versus aspartate aminotransferase (AST), were chosen for inclusion when the number of variables allowed in the MVA model was limited due to our small sample size. For the MVA, only variables with p-values < 0.05 were considered significant.

Results

Sample statistics: Forty SCD patients (27 adults, 13 children) with COVID-19 were identified. Our SCD catchment in the year 2020 was 1098 unique patients (578 adults, 520 children), translating to a symptomatic infection rate of 3.3% (36 symptomatic patients among 40; adult rate 4.7%, peds rate 2.5%). Patient characteristics are shown in Table 1, stratified by adult and pediatric groups. Of the 40 patients, 85% (23/27) of adults and 69% (9/13) of children were hospitalized; of the inpatients, 17% (4/23) adults and 22% (2/9) children went to the ICU. SCD severity scores were significantly lower in children compared to adults (mean 0.06 ± 0.05 versus 0.24 ± 0.14, Wilcoxon rank sum test, $p < 0.001$), with the Spearman correlation coefficient between age and SCD severity score being 0.84. Genotype distribution only in adults (45% SS, 33% SC, and 22% Sβ thalassemia (5 Sβ^0 and 2 Sβ^+)) differed significantly from the published population distribution of 75.6% SS, 17.8% SC, and 5.4% Sβ (binomial exact test, $p < 0.05$)[20].

Presenting symptoms were typical of SCD and/or COVID-19 infection and included fever, pain, shortness of breath and altered mental status. Of the 4 asymptomatic patients, the 3 adult inpatients (admitted for vaso-occlusive crisis) were tested per standard hospital admission protocol and the pediatric outpatient was tested due to known exposure to COVID-19.

Clinical course: Since COVID-19 infection may precipitate or exacerbate SCD-related complications[8,10,21], complications were classified as SCD-related or COVID-19-related as per Table 2; outpatients had no complications. Of the 15% (4 of 27) adults who experienced COVID-19 complications, all went to the ICU and required intubation, whereas no children had COVID-19 related complications. SCD-related complications were diagnosed in 52% (14) of adult and 38% (5) of pediatric patients (Fisher's exact test, p=0.5). The mortality rate for our SCD cohort with COVID-19 (n=40) was 2.5% (1 adult ICU patient) and the in-hospital mortality rate (hospitalized patients: n=32), was 3.1%. Hospitalization status was associated with both SCD-related and COVID-19 severity, with a strong association between hospitalization status and COVID-19 severity score (Fisher's exact test, p=<0.001). Hospitalization status and ICU admission were therefore chosen as relevant outcomes for univariate and multivariable analysis; control groups were SCD patients with COVID-19 who were outpatients and floor inpatients, respectively.

Univariate and multivariable analysis: The p-values for the univariate analyses (UVA) of the two outcome measures are shown in Supplemental Table 1. Results of the MVA are shown in Table 3. For hospitalization status, the only significant variable was admission Hb (OR=0.40, 95% CI: 0.15, 0.78): that is, every 1 gm/dL increase in Hb decreased the odds of hospital admission by 60%. In hospitalized patients, ICU admission was associated with 3 variables: HU use, health care worker status and high immature granulocytes at admission. Using HU

decreased the odds of ICU admission by 17% (odds ratio: 0.83, CI: 0.71 − 0.96). HU use was associated with higher HbF levels (mean $\pm$ SD = 10.6 $\pm$ 6.1 HU versus 6.0 $\pm$5.6 no HU, Wilcoxon rank sum test p=0.03, Supplemental Table 2), indicative of HU compliance. Being a health care worker increased the odds of ICU admission by 84% (odds ratio: 1.84, CI: 1.43-2.37). Every 1000/uL increase in the count of immature granulocytes increased the odds of ICU admission by 45% (odds ratio: 1.45, CI 1.32-1.59).

Discussion

Our study in SCD patients examined their rates of COVID-19 infection and related hospitalization, ICU admission, cohort mortality, and in-hospital mortality. We also performed a MVA of risk factors for COVID-19 related severity, as defined by need for hospitalization or ICU admission. Our symptomatic infection rate was 3.3%, compared to a symptomatic infection rate median of 8.6% in the general U.S. population[22]. Our data contrasts with a meta-analysis finding a higher incidence of COVID-19 infection, but with a wide confidence interval, than in the general population,[2] and may be related to our patients' compliance with COVID-19 mitigation measures such as social distancing (personal observation of one of our SCD physicians, Dr. Shi), as lack of access to care and testing is unlikely given that all patients included in the study had been seen in the year 2020. Interestingly, the sickle genotype distribution of our COVID-19 infected patients was significantly different from the SCD US population distribution.[20] This may be related to SARS-CoV-2 diagnostic bias toward symptomatic patients and is consistent with previous reports[5,21] of higher morbidity or mortality in the SC/Sβ^+ genotypes. Of note, as previously reported[1], our patients with SC/Sβ^+ genotypes were less likely to be on HU than SS/Sβ^0 genotypes (Fisher's exact test, p-value=0.002). While

our 19% ICU admission rate is similar to the U.S. general population rate[23], our 80% overall hospitalization is higher than the U.S. general population rate of 2%[22] but compatible with previously reported ranges in SCD between 41-76% for hospitalization and 11-20% for ICU[1,3-5,21]. Our higher-end hospitalization rate may reflect a conservative approach with our SCD patients. Also notable however, as reported previously[8,21], is that a majority of hospitalizations were for SCD-related rather than COVID-19 related complications, most frequently acute painful episodes. In fact, pediatric patients had no COVID-19 related complications, consistent with previously published milder courses in pediatric SCD patients[3,5,9] Our cohort mortality of 2.5% is on the low end of the 3-10% range in SCD previously reported; [1,4,5,21] higher than the U.S. general population symptomatic fatality of 1.1%[22] but perhaps not higher when specifically compared to a U.S. black population[4,8]. Our in-hospital mortality rate of 3.1% was lower than the 8% found in a nearby geographic area[8] and again, may reflect a conservative approach to hospitalize our SCD patients.

In regard to risk factors for COVID-19 related severity, the only variable that held up to MVA for the outcome of hospitalization was admission Hb; this is consistent with previous findings of a significant Hb decrease from baseline for SCD patients requiring hospitalization[1] and studies that reported Hb as a strong predictor of COVID-19 related severity or mortality in the general population[16,24,25] For the outcome of ICU admission, 3 variables remained significant in the MVA: HCW employment, HU use, and immature granulocyte count on admission. HCW employment has not been previously reported as a risk factor in SCD ICU admission but has been associated with COVID-19 morbidity in the general US population as well as comprehensive meta-analysis.[13,14]. HU use has been reported to reduce morbidity in SCD in one report[1] but not others.[10,21] It is biologically plausible that HU might decrease morbidity from

COVID-19 infection due to reduction of coagulation and neutrophil and endothelial cell activation.[26-28] Finally, the level of immature granulocytes has not been previously reported as a risk factor in SCD ICU admission, but is associated with disease severity and ICU admission in the general population[15,17].

In summary, our findings are compatible with SCD patients having more complications upon COVID-19 infection than the general population as measured by hospitalization rate. MVA suggests that patients should be placed on hydroxyurea to increase their Hb and perhaps lower their neutrophil counts, and that health care workers with SCD may warrant special safety precautions. The advantage to our study is our thorough capture of all SCD patients across multiple sites of the largest health system in New York State diagnosed with COVID-19, in a state heavily affected by COVID-19 at the time and before COVID-19 vaccination became available. Nevertheless, our study is limited by its small sample size and its UVA and MVA limited to variables with ≤ 10% missing values.

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Table 1. Overview of SCD patients with COVID-19 (n=40)*	Inpatients (n=32)				Outpatients (n=8)	
	ICU (n=6)		Floor (n=26)			
	Adult (n=4)	Peds (n=2)	Adult (n=19)	Peds (n=7)	Adult (n=4)	Peds (n=4)
Mean age (SD)	45 (14.9)	9.5 (10.6)	39.4 (14.2)	10.1 (6.3)	32.0 (8.9)	14.8 (0.5)
% Female	75%	0%	63%	43%	100%	25%
Mean body mass index (SD)	21.4 (3.2)	14.8 (1.2)	25.9 (6.4)	20.2 (4.2)	24.6 (2.4)	23.6 (1.5)
Mean SCD severity score (SD)	0.33 (0.24)	0.12 (0.13)	0.25 (0.13)	0.05 (0.01)	0.17 (0.06)	0.06 (0.02)
% on hydroxyurea	25%	50%	74%	57%	none	50%
% healthcare worker	50%	none	5%	none	none	none
% black race	50%	50%	58%	86%	100%	100%
% sickle genotype	50% SS, 50% SC	100% SS	47% SS, 21% SC 21% Sβ^0, 11% Sβ^+	86% SS 14% SC	25% SS 75% SC	50% SS, 25% SC, 25% Sβ^0

Comorbidities	% per category	Stroke: 25% Smoking: 25%	none	Hypertension: 16% Coronary artery disease: 5% Aortic coarctation: 5% Venous thrombosis: 21% Asthma: 16% Stroke: 11% Trigeminal neuralgia 5% Smoking: 11% End stage renal disease: 11%	Asthma: 29 %	Mitral valve replacement: 25%	Atrial tachycardia: 25% Asthma: 25% Stroke 25%

				Systemic...		
				HIV: 5%		
	Mean # (SD)	1 (0.5)	0 (0)	1 (0.9)	0.3 (0.5)	0.3 (0.4)	0.8 (0.4)

Presenting symptoms	% fever	75%	50%	26%	71%	75%	75%
	% pain	50%	50%	74%	14%	25%	25%
	% SOB	25%	none	42%	14%	25%	25%
	% AMS	25%	none	11%	none	none	none
	Mean # (SD)	2 (0.8)	1 (0.0)	2 (0.7)	1 (0.5)	1 (0.8)	1 (0.8)
COVID-19 severity grade		100% critical	100% severe	16% asymptomatic 37% mild 37% moderate 10% severe	43% mild 28.5% moderate 28.5% severe	100% mild	25% asymptomatic 75% mild

*SD= standard deviation

Table 2. Patients with Complications*		N	Floor (n=26)															ICU (n=6)					
			Adult (n=13/19)												Peds (n=3/7)			Adult (n=4/4)				Peds (n=2/2)	
COVID-19 related complications	Respiratory distress & intubation	4																x	x	x	x		
	Cardiomyopathy	1																			x		
	Pancreatitis	1																			x		
	Stroke	1																	x				
	Cytokine release syndrome	1																	x				
	Acute kidney injury	4			x													x		x	x		
	Pulmonary emboli	1		x																			
SCD-related complications	Acute pain episode	14	x		x	x	x	x	x	x	x	x	x		x				x			x	x
	Acute chest syndrome	7			x					x	x		x						x			x	x
	Splenic complication‡	2												x				x					
	Priapism	1	x																				
COVID-19 treatments	Enoxaparin	7				x		x			x	x	x					x			x		

		n	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15†	16	17	18	19	20	21
	Antibiotic	13	x	x		x			x			x	x		x	x	x		x	x	x	x	
	Remdesivir	3											x	x									x
	Steroid	2											x										x
	Anakinra	1													x								
SCD treatments	Simple transfusion	14		x		x		x		x		x	x	x		x	x		x	x	x	x	x
	Exchange transfusion	3											x									x	x
	Hydroxyurea (outpatient)	11	x	x	x			x		x	x	x	x	x	x			x					
	Crizanlizumab (outpatient)	1										x											
	L-glutamine (outpatient)	1										x											

*Each column represents an individual patient who experienced a complication (marked with an x)

The patient who died is highlighted in gray.

‡ Sequestration in peds patient, infarct in adult patient

Table 3. Results of Multivariable Analyses				
Outcome	**Parameter**	**Odds Ratio**	**95% Confidence Interval**	**p-value**
Hospital admission	Admission Hb (g/dL)	0.40	0.15, 0.78	0.026
ICU admission	Health care worker (yes/no)	1.84	1.43, 2.37	0.0001
	Hydroxyurea use (yes/no)	0.83	0.71, 0.96	0.017
	Admission immature granulocytes [K/μL]	1.45	1.32, 1.59	<0.0001